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1998wo-us14552.ap.	1

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Search History

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DB=EPAB,JPAB,DWPI; PLUR=YES; OP=OR			
L3	1998wo-us14552.ap.	1	L3
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L1	1998wo-us12456.ap,prai.	80	L1

END OF SEARCH HISTORY

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Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: RTD RECEPTOR

(57) Abstract

Novel polypetides, designated RTD, which are capable of binding Apo–2 ligand are provided. RTD are receptors for the tumor necrosis factor (TNF), belonging to the family of trail – receptors. They are inhibitors of APO2L– induced apoptosis. They act as decoy receptors, lacking an intracellular signalling death domain. Compositions including RTD chimeras, nucleic acid encoding RTD, and antibodies to RTD are also provided.

apoptosis. Similar results were obtained with HeLa cells (data not shown). These results suggest that RTD does not signal cell death and demonstrate that RTD can inhibit Apo-2 ligand function when it is expressed at high levels.

EXAMPLE 5

Northern Blot Analysis

Expression of RTD mRNA in human tissues was examined by Northern blot analysis. Human RNA blots were hybridized to a 200 bp ^{32}P-labelled DNA probe based on the 3' untranslated region of the RTD. The probe was generated by PCR with the following oligonucleotide primers: CTTCAGGAAACCAGAGCTTCCCTC (SEQ ID NO:4); TTCTCCCGTTTGCTTATCACACGC (SEQ ID NO:5). Probes specific for beta-actin were used as controls. Human fetal RNA blot MTN (Clontech) and human adult RNA blot MTN-II (Clontech) were incubated with the DNA probes. Blots were incubated with the probes in hybridization buffer (5X SSPE; 2X Denhardt's solution; 100 mg/mL denatured sheared salmon sperm DNA; 50% formamide; 2% SDS) for 60 hours at 42°C. The blots were washed several times in 2X SSC; 0.05% SDS for 1 hour at room temperature, followed by a 30 minute wash in 0.1X SSC; 0.1% SDS at 50°C. The blots were developed after overnight exposure by phosphorimager analysis (Fuji).

As shown in Fig. 4, a single RTD mRNA transcript of about 4 kb was detected. This transcript was expressed in fetal kidney, liver and lung, and in multiple adult tissues, particularly in testis and kidney. This mRNA expression pattern differs from that of DR4, DR5 and DcR1. DR4 and DcR1 are particularly abundant in peripheral blood leukocytes and spleen, and DR5 is most abundant in ovary, liver and lung.

EXAMPLE 6

Chromosomal Localization of the RTD, DR5, DR4 and DcR1 genes

Chromosomal localization of these human genes was examined by radiation hybrid (RH) panel analysis. RH mapping was performed by PCR using a human-mouse cell radiation hybrid panel (Research Genetics) and primers based on the coding region of the DR5 cDNA [Gelb et al., Hum. Genet., 98:141 (1996)]. Analysis of the PCR data using the Stanford Human Genome Center Database and the Whitehead Institute for Biomedical Research/MIT Center for Genome Research indicates that DR5 is linked to the marker D8S481, with an LOD of 11.05; D8S481 is linked in turn to D8S2055, which maps to human chromosome 8p21. A similar analysis of DR4 showed that DR4 is linked to the marker D8S2127 (with an LOD of 13.00), which maps also to human chromosome 8p21. Analysis of DcR1 using radiation hybrid panel examination showed that the DcR1 gene is linked to the marker WI-6536, which in turn is linked to D8S298, which maps also to human chromosome 8p21 and is nested between D8S2005 and D8S2127.

Using a primer based on the 3' untranslated region of the RTD cDNA, an analysis revealed that RTD was linked to marker SHGC-33989 (LOD of 7.2). Marker SHGC-33989 is linked to D8S2055, which maps to human chromosome 8p21. Thus, the human genes for RTD, DR5, DcR1 and DR4, all map to chromosome 8p21.

Deposit of Material

The following materials have been deposited with the American Type Culture Collection, 10801 University Blvd., Manassas, Virginia, USA (ATCC):

Material	ATCC Dep. No.	Deposit Date
pRK5-35663	209201	Aug. 18, 1997
pRK5-35664	209202	Aug. 18, 1997

This deposit was made under the provisions of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purpose of Patent Procedure and the Regulations thereunder (Budapest Treaty). This assures maintenance of a viable culture of the deposit for 30 years from the date of deposit. The deposit will be made available by ATCC under the terms of the Budapest Treaty, and subject to an agreement between Genentech, Inc. and ATCC, which assures permanent and unrestricted availability of the progeny of the culture of the deposit to the public upon issuance of the pertinent U.S. patent or upon laying open to the public of any U.S. or foreign patent application, whichever comes first, and assures availability of the progeny to one determined by the U.S. Commissioner of Patents and Trademarks to be entitled thereto according to 35 USC §122 and the Commissioner's rules pursuant thereto (including 37 CFR §1.14 with particular reference to 886 OG 638).

The assignee of the present application has agreed that if a culture of the materials on deposit should die or be lost or destroyed when cultivated under suitable conditions, the materials will be promptly replaced on notification with another of the same. Availability of the deposited material is not to be construed as a license to practice the invention in contravention of the rights granted under the authority of any government in accordance with its patent laws.

The foregoing written specification is considered to be sufficient to enable one skilled in the art to practice the invention. The present invention is not to be limited in scope by the construct deposited, since the deposited embodiment is intended as a single illustration of certain aspects of the invention and any constructs that are functionally equivalent are within the scope of this invention. The deposit of material herein does not constitute an admission that the written description herein contained is inadequate to enable the practice of any aspect of the invention, including the best mode thereof, nor is it to be construed as limiting the scope of the claims to the specific illustrations that it represents. Indeed, various modifications of the invention in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description and fall within the scope of the appended claims.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT: Genentech, Inc.

(ii) TITLE OF INVENTION: RTD Receptor

(iii) NUMBER OF SEQUENCES: 5

(iv) CORRESPONDENCE ADDRESS:
(A) ADDRESSEE: Genentech, Inc.
(B) STREET: 1 DNA Way
(C) CITY: South San Francisco
(D) STATE: California
(E) COUNTRY: USA
(F) ZIP: 94080

(v) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: 3.5 inch, 1.44 Mb floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: WinPatin (Genentech)

(vi) CURRENT APPLICATION DATA:
(A) APPLICATION NUMBER:
(B) FILING DATE: 14-Jul-1998
(C) CLASSIFICATION:

(vii) PRIOR APPLICATION DATA:
(A) APPLICATION NUMBER: 08/918874
(B) FILING DATE: 26-Aug-1997

(viii) ATTORNEY/AGENT INFORMATION:
(A) NAME: Marschang, Diane L.
(B) REGISTRATION NUMBER: 35,600
(C) REFERENCE/DOCKET NUMBER: P1129R1PCT

(ix) TELECOMMUNICATION INFORMATION:
(A) TELEPHONE: 650/225-5416
(B) TELEFAX: 650/952-9881

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 386 amino acids
(B) TYPE: Amino Acid
(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

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Met Gly Leu Trp Gly Gln Ser Val Pro Thr Ala Ser Ser Ala Arg
 1               5                  10                  15

Ala Gly Arg Tyr Pro Gly Ala Arg Thr Ala Ser Gly Thr Arg Pro
            20                  25                  30

Trp Leu Leu Asp Pro Lys Ile Leu Lys Phe Val Val Phe Ile Val
            35                  40                  45
```

Ala Val Leu Leu Pro Val Arg Val Asp Ser Ala Thr Ile Pro Arg
50 55 60

Gln Asp Glu Val Pro Gln Gln Thr Val Ala Pro Gln Gln Gln Arg
65 70 75

Arg Ser Leu Lys Glu Glu Glu Cys Pro Ala Gly Ser His Arg Ser
80 85 90

Glu Tyr Thr Gly Ala Cys Asn Pro Cys Thr Glu Gly Val Asp Tyr
95 100 105

Thr Ile Ala Ser Asn Asn Leu Pro Ser Cys Leu Leu Cys Thr Val
110 115 120

Cys Lys Ser Gly Gln Thr Asn Lys Ser Ser Cys Thr Thr Thr Arg
125 130 135

Asp Thr Val Cys Gln Cys Glu Lys Gly Ser Phe Gln Asp Lys Asn
140 145 150

Ser Pro Glu Met Cys Arg Thr Cys Arg Thr Gly Cys Pro Arg Gly
155 160 165

Met Val Lys Val Ser Asn Cys Thr Pro Arg Ser Asp Ile Lys Cys
170 175 180

Lys Asn Glu Ser Ala Ala Ser Ser Thr Gly Lys Thr Pro Ala Ala
185 190 195

Glu Glu Thr Val Thr Thr Ile Leu Gly Met Leu Ala Ser Pro Tyr
200 205 210

His Tyr Leu Ile Ile Ile Val Val Leu Val Ile Ile Leu Ala Val
215 220 225

Val Val Val Gly Phe Ser Cys Arg Lys Lys Phe Ile Ser Tyr Leu
230 235 240

Lys Gly Ile Cys Ser Gly Gly Gly Gly Gly Pro Glu Arg Val His
245 250 255

Arg Val Leu Phe Arg Arg Arg Ser Cys Pro Ser Arg Val Pro Gly
260 265 270

Ala Glu Asp Asn Ala Arg Asn Glu Thr Leu Ser Asn Arg Tyr Leu
275 280 285

Gln Pro Thr Gln Val Ser Glu Gln Glu Ile Gln Gly Gln Glu Leu
290 295 300

Ala Glu Leu Thr Gly Val Thr Val Glu Xaa Pro Glu Glu Pro Gln
305 310 315

Arg Leu Leu Glu Gln Ala Glu Ala Glu Gly Cys Gln Arg Arg Arg
320 325 330

Leu Leu Val Pro Val Asn Asp Ala Asp Ser Ala Asp Ile Ser Thr

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                    335                 340                 345

Leu Leu Asp Ala Ser Ala Thr Leu Glu Glu Gly His Ala Lys Glu
                    350                 355                 360

Thr Ile Gln Asp Gln Leu Val Gly Ser Glu Lys Leu Phe Tyr Glu
                    365                 370                 375

Glu Asp Glu Ala Gly Ser Ala Thr Ser Cys Leu
                    380                 385 386
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(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2082 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

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CCAACTGCAC CTCGGTTCTA TCGATTGAAT TCCCCGGGGA TCCTCTAGAG 50

ATCCCTCGAC CTCGACCCAC GCGTCCGGAA CCTTTGCACG CGCACAAACT 100

ACGGGGACGA TTTCTGATTG ATTTTTGGCG CTTTCGATCC ACCCTCCTCC 150

CTTCTC  ATG GGA CTT TGG GGA CAA AGC GTC CCG ACC GCC 189
        Met Gly Leu Trp Gly Gln Ser Val Pro Thr Ala
          1               5                  10

TCG AGC GCT CGA GCA GGG CGC TAT CCA GGA GCC AGG ACA 228
Ser Ser Ala Arg Ala Gly Arg Tyr Pro Gly Ala Arg Thr
             15                  20

GCG TCG GGA ACC AGA CCA TGG CTC CTG GAC CCC AAG ATC 267
Ala Ser Gly Thr Arg Pro Trp Leu Leu Asp Pro Lys Ile
 25                  30                  35

CTT AAG TTC GTC GTC TTC ATC GTC GCG GTT CTG CTG CCG 306
Leu Lys Phe Val Val Phe Ile Val Ala Val Leu Leu Pro
         40                  45                  50

GTC CGG GTT GAC TCT GCC ACC ATC CCC CGG CAG GAC GAA 345
Val Arg Val Asp Ser Ala Thr Ile Pro Arg Gln Asp Glu
                 55                  60

GTT CCC CAG CAG ACA GTG GCC CCA CAG CAA CAG AGG CGC 384
Val Pro Gln Gln Thr Val Ala Pro Gln Gln Gln Arg Arg
     65                  70                  75

AGC CTC AAG GAG GAG GAG TGT CCA GCA GGA TCT CAT AGA 423
Ser Leu Lys Glu Glu Glu Cys Pro Ala Gly Ser His Arg
             80                  85

TCA GAA TAT ACT GGA GCC TGT AAC CCG TGC ACA GAG GGT 462
Ser Glu Tyr Thr Gly Ala Cys Asn Pro Cys Thr Glu Gly
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     90                  95                 100

     GTG GAT TAC ACC ATT GCT TCC AAC AAT TTG CCT TCT TGC 501
     Val Asp Tyr Thr Ile Ala Ser Asn Asn Leu Pro Ser Cys
             105                 110                 115

5    CTG CTA TGT ACA GTT TGT AAA TCA GGT CAA ACA AAT AAA 540
     Leu Leu Cys Thr Val Cys Lys Ser Gly Gln Thr Asn Lys
                     120                 125

     AGT TCC TGT ACC ACG ACC AGA GAC ACC GTG TGT CAG TGT 579
     Ser Ser Cys Thr Thr Thr Arg Asp Thr Val Cys Gln Cys
10       130                 135                 140

     GAA AAA GGA AGC TTC CAG GAT AAA AAC TCC CCT GAG ATG 618
     Glu Lys Gly Ser Phe Gln Asp Lys Asn Ser Pro Glu Met
                 145                 150

     TGC CGG ACG TGT AGA ACA GGG TGT CCC AGA GGG ATG GTC 657
15   Cys Arg Thr Cys Arg Thr Gly Cys Pro Arg Gly Met Val
     155                 160                 165

     AAG GTC AGT AAT TGT ACG CCC CGG AGT GAC ATC AAG TGC 696
     Lys Val Ser Asn Cys Thr Pro Arg Ser Asp Ile Lys Cys
             170                 175                 180

20   AAA AAT GAA TCA GCT GCC AGT TCC ACT GGG AAA ACC CCA 735
     Lys Asn Glu Ser Ala Ala Ser Ser Thr Gly Lys Thr Pro
                     185                 190

     GCA GCG GAG GAG ACA GTG ACC ACC ATC CTG GGG ATG CTT 774
     Ala Ala Glu Glu Thr Val Thr Thr Ile Leu Gly Met Leu
25       195                 200                 205

     GCC TCT CCC TAT CAC TAC CTT ATC ATC ATA GTG GTT TTA 813
     Ala Ser Pro Tyr His Tyr Leu Ile Ile Ile Val Val Leu
                 210                 215

     GTC ATC ATT TTA GCT GTG GTT GTG GTT GGC TTT TCA TGT 852
30   Val Ile Ile Leu Ala Val Val Val Val Gly Phe Ser Cys
     220                 225                 230

     CGG AAG AAA TTC ATT TCT TAC CTC AAA GGC ATC TGC TCA 891
     Arg Lys Lys Phe Ile Ser Tyr Leu Lys Gly Ile Cys Ser
             235                 240                 245

35   GGT GGT GGA GGA GGT CCC GAA CGT GTG CAC AGA GTC CTT 930
     Gly Gly Gly Gly Gly Pro Glu Arg Val His Arg Val Leu
                     250                 255

     TTC CGG CGG CGT TCA TGT CCT TCA CGA GTT CCT GGG GCG 969
     Phe Arg Arg Arg Ser Cys Pro Ser Arg Val Pro Gly Ala
40       260                 265                 270

     GAG GAC AAT GCC CGC AAC GAG ACC CTG AGT AAC AGA TAC 1008
     Glu Asp Asn Ala Arg Asn Glu Thr Leu Ser Asn Arg Tyr
                 275                 280
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TTG CAG CCC ACC CAG GTC TCT GAG CAG GAA ATC CAA GGT 1047
Leu Gln Pro Thr Gln Val Ser Glu Gln Glu Ile Gln Gly
285                 290                 295

CAG GAG CTG GCA GAG CTA ACA GGT GTG ACT GTA GAG TYG 1086
Gln Glu Leu Ala Glu Leu Thr Gly Val Thr Val Glu Xaa
        300                 305                 310

CCA GAG GAG CCA CAG CGT CTG CTG GAA CAG GCA GAA GCT 1125
Pro Glu Glu Pro Gln Arg Leu Leu Glu Gln Ala Glu Ala
                315                 320

GAA GGG TGT CAG AGG AGG AGG CTG CTG GTT CCA GTG AAT 1164
Glu Gly Cys Gln Arg Arg Arg Leu Leu Val Pro Val Asn
    325                 330                 335

GAC GCT GAC TCC GCT GAC ATC AGC ACC TTG CTG GAT GCC 1203
Asp Ala Asp Ser Ala Asp Ile Ser Thr Leu Leu Asp Ala
            340                 345

TCG GCA ACA CTG GAA GAA GGA CAT GCA AAG GAA ACA ATT 1242
Ser Ala Thr Leu Glu Glu Gly His Ala Lys Glu Thr Ile
350                 355                 360

CAG GAC CAA CTG GTG GGC TCC GAA AAG CTC TTT TAT GAA 1281
Gln Asp Gln Leu Val Gly Ser Glu Lys Leu Phe Tyr Glu
        365                 370                 375

GAA GAT GAG GCA GGC TCT GCT ACG TCC TGC CTG TGAAAG 1320
Glu Asp Glu Ala Gly Ser Ala Thr Ser Cys Leu
                380                 385 386

AATCTCTTCA GGAAACCAGA GCTTCCCTCA TTTACCTTTT CTCCTACAAA 1370

GGGAAGCAGC CTGGAAGAAA CAGTCCAGTA CTTGACCCAT GCCCCAACAA 1420

ACTCTACTAT CCAATATGGG GCAGCTTACC AATGGTCCTA GAACTTTGTT 1470

AACGCACTTG GAGTAATTTT TATGAAATAC TGCGTGTGAT AAGCAAACGG 1520

GAGAAATTTA TATCAGATTC TTGGCTGCAT AGTTATACGA TTGTGTATTA 1570

AGGGTCGTTT TAGGCCACAT GCGGTGGCTC ATGCCTGTAA TCCCAGCACT 1620

TTGATAGGCT GAGGCAGGTG GATTGCTTGA GCTCGGGAGT TTGAGACCAG 1670

CCTCATCAAC ACAGTGAAAC TCCATCTCAA TTTAAAAAGA AAAAAAGTGG 1720

TTTTAGGATG TCATTCTTTG CAGTTCTTCA TCATGAGACA AGTCTTTTTT 1770

TCTGCTTCTT ATATTGCAAG CTCCATCTCT ACTGGTGTGT GCATTTAATG 1820

ACATCTAACT ACAGATGCCG CACAGCCACA ATGCTTTGCC TTATAGTTTT 1870

TTAACTTTAG AACGGGATTA TCTTGTTATT ACCTGTATTT TCAGTTTCGG 1920

ATATTTTTGA CTTAATGATG AGATTATCAA GACGTACCCC TATGCTAAGT 1970
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CATGAGCATA TGGACTTACG AGGGTTCGAC TTAGAGTTTT GAGCTTTAAG 2020

ATAGGATTAT TGGGGGCTTA CCCCCACCTT AATTAGAAGA AACATTTTAT 2070

ATTGCTTTAC TA 2082

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

CATAAAAGTT CCTGCACCAT GACCAGAGAC ACAGTGTGTC AGTGTAAAGA 50

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

CTTCAGGAAA CCAGAGCTTC CCTC 24

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

TTCTCCCGTT TGCTTATCAC ACGC 24